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In this supplement: Enterovirus D68 and influenza

Last fall, enterovirus D68– an emerging virus causing respiratory illness largely in children – was documented in Canada, the United States as well as parts of Europe and Asia. In this supplement, read about the first epidemiologic summary of hospitalized pediatric cases in Canada, and the review on non-polio-enteroviruses. See the link to the report on the two cases of H7N9 in Canada, get a snapshot of what influenza is like in Canada this year and read the summaries of two studies on the effectiveness of the 2014/15 influenza vaccine.

Surveillance

Surveillance summary of hospitalized pediatric enterovirus D68 cases in Canada, September 2014 2
Edwin JJ, Reyes Domingo F, Booth TF, Mersereau T, Skowronski DM, Chambers C et al.

FluWatch summary: February 8–14, 2015 (Week 6) 9
Lee L, Saboui M, Mersereau T

Review

National surveillance for non-polio enteroviruses in Canada: Why is it important? 11
Booth TF, Grudeski E, McDermid A

Overview

Canadian vaccine research networks: Vaccine safety resources for Canada..... 18
McCarthy J, Halperin SA, Bettinger JA, Langley JM, Crowcroft NS, Deeks S et al.

ID News

EV-D68 and influenza vaccine effectiveness..... 24

Useful links

World Health Organization. **Human infection with avian influenza A(H7N9) virus – Canada**. Disease Outbreak News. 1 February 2015.
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Moghadas S, Laskowski M. **A logical modelling framework for influenza infection**. National Collaborating Centre for Infectious Diseases, 2014 Sep.
https://cdn.metricmarketing.ca/www.nccid.ca/files/Influenza/ModelFrameFLU_FINAL.pdf

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Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

Surveillance summary of hospitalized pediatric enterovirus D68 cases in Canada, September 2014

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Abstract

Background: Enterovirus D68 (EV-D68) has been detected infrequently and has not been associated with severe disease in Canada. In the early fall of 2014, following an unusual case increase in the United States, clusters of EV-D68 among children and some adults manifesting severe symptoms were reported in Canada.

Objective: To provide an initial epidemiological summary of pediatric cases hospitalized with EV-D68 in Canada.

Methods: A time-limited surveillance pilot was conducted collecting information on pediatric cases (less than 18 years of age) hospitalized with EV-D68 between September 1 and 30, 2014.

Results: In total, 268 cases were reported from Ontario (n=210), Alberta (n=45), and British Columbia (n=13). Of the 268 reported cases, 64.9% (n=174) were male; the sex difference was statistically significant ($p<0.01$). Age was reported for 255 cases, with a mean age for males of 5.4 years and for females of 5.3 years. For cases with data available, 6.8% (18/266) were admitted to an intensive care unit. Of those where clinical illness was recorded, respiratory illness alone was present in 98.3% (227/231), neurologic illness alone was present in 0.4% (n=1), and both illnesses were present in 0.9% of cases (n=2); cases with neither respiratory nor neurologic illness were rare (n=1). Of the 90 cases with additional clinical information available, 43.3% were reported as having asthma. No deaths were reported among the 268 cases.

Conclusion: The EV-D68 outbreak in Canada in September 2014 represents the beginning of a novel outbreak associated with severe illness in children. These findings provide the first epidemiological summary of severe cases of EV-D68 as an emergent respiratory pathogen in Canada. The continued investigation of this pathogen is necessary to build on these results and capture the full spectrum of associated illness.

Introduction

Enterovirus D68 or EV-D68 (genus enterovirus) is a non-polio enterovirus of the Picornaviridae family (1). It was first discovered in 1962 after it was isolated from four children ill with pneumonia and bronchiolitis in California (2). Historically, detections of EV-D68 have been infrequent (3). From 1970 to 2005, the United States National Enterovirus Surveillance System identified EV-D68 in only 26 of 49,637 (0.1%) laboratory-typed enterovirus specimens identified during this 36-year period (4). In Canada, a total of 82 cases of EV-D68 were identified by the National Microbiology Laboratory from 1999 to 2013 (5).

Since 2008, several outbreaks of EV-D68 have been reported internationally, including in the Philippines (2008–2009) (6), Japan (2010) (7, 8), the Netherlands (2010) (9, 10), and the United States (2009–2010) (11, 12). Reported illness ranged from mild symptoms associated with respiratory illness (fever, runny nose, sneezing, coughing, and body and muscle aches) to severe disease, primarily pneumonia and bronchiolitis, requiring intensive care (12). Infections were reported in both children and adults; however, children aged less than 1 month to 4 years old were most commonly affected. Children with underlying respiratory disease (e.g., asthma, wheezing, and bronchiolitis) and immunocompromised adults have been reported to experience more severe disease (13, 14). The epidemiology and full spectrum of disease caused by EV-D68 remains unclear (12, 13), primarily due to its infrequent detection. However, its recent emergence as a pathogen with outbreak potential associated with severe illness (7–12) provides impetus for investigation.

Event description

In mid-August 2014, the U.S. Centers for Disease Control and Prevention (CDC) was notified of increases in severe respiratory illness in children in Kansas City and Chicago. Further testing identified EV-D68 as the predominant etiologic agent detected (13). From mid-August to December 11, 2014, the outbreak had spread across the country resulting in 1,149 laboratory-confirmed EV-D68 cases and 12 deaths reported from 48 states and the District of Columbia (15). The CDC has also been investigating reports of children presenting with acute flaccid myelitis associated with EV-D68 infection. Investigations are still ongoing to determine the role, if any, of EV-D68 infection among cases of neurologic illness identified during the same period (15, 16).

In September 2014, some Canadian jurisdictions reported laboratory-confirmed EV-D68 cases, including an association with neurologic findings (17, 18). As of December 15, 2014, laboratory-confirmed cases of EV-D68, primarily among those 18 years of age and younger have been detected in all ten provinces and one territory in Canada. EV-D68 is not a nationally notifiable disease in Canada, and thus little is known of the scale of its impact as a seasonal respiratory virus. Heightened awareness among public health and clinicians following the U.S. clusters likely contributed to the initial detection of cases in Canada.

Given the emergence of cases in Canada, and the limited knowledge of the epidemiology and full spectrum of disease caused by EV-D68, the Public Health Agency of Canada (PHAC), in collaboration with participating provincial and territorial (P/T) public health organizations, initiated a time-limited EV-D68 Severe Outcomes Surveillance Pilot in September 2014. The purpose of this article is to provide an epidemiological summary of hospitalized pediatric cases from the emergent stages of the EV-D68 outbreak in Canada.

Investigations

In September 2014, all provincial health agencies were invited to participate in the EV-D68 Severe Outcomes Surveillance Pilot. The following P/T health agencies and health centres participated in the surveillance pilot: Alberta Health; British Columbia Centre for Disease Control (BCCDC); New Brunswick Department of Health; Yukon Health and Social Services; Northwest Territories Department of Health and Social Services; Nunavut Department of Health; and Ontario (Public Health Ontario (PHO); the Children's Hospital of Eastern Ontario (CHEO); and the Hamilton Regional Laboratory Medicine Program (HRLMP), serving Hamilton Health Sciences, St. Joseph's Healthcare Hamilton, and other community hospitals in South Central Ontario). Management of the pilot project and the epidemiological analysis were conducted by PHAC's Centre for Immunization and Respiratory Infectious Diseases.

Case definition

Cases were defined as persons ≤18 years of age who were hospitalized and tested positive for EV-D68 infection by polymerase chain reaction (PCR) testing and/or genetic sequencing of the virus using standard enterovirus genotyping methods (19,20), or an EV-D68 specific real-time PCR (21), from any clinical specimen collected in September 2014.

Data collection

The following information was requested for all cases in aggregate form or in a de-identified line list: specimen collection date; sex; age; admission to an intensive care unit (ICU); clinical presentation (e.g., respiratory illness and/or neurologic illness); other clinical information (asthma); and outcomes (e.g., survived/died). Data collection was performed, where possible, using an enhanced surveillance case reporting form (CRF) (available upon request).

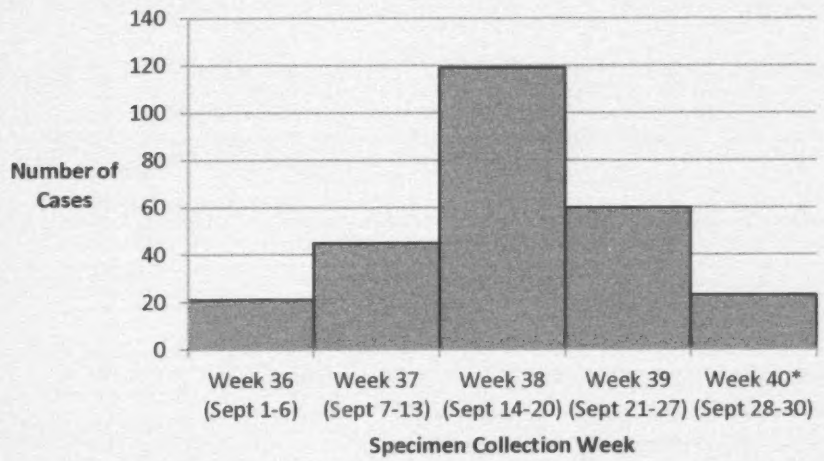
Data analysis

Basic descriptive analyses were performed to generate an epidemiological summary of hospitalized EV-D68 cases. Differences between groups (males versus females, and <5 years of age versus 5–18 years) were tested using Chi-square statistic with the assumption that EV-D68 is expected to infect an equal rate of individuals (by sex and age) as the population distribution in the jurisdictions reporting the cases. Expected values were calculated using population estimates for 2014 from Statistics Canada (22).

Assessment

Between September 1 and 30, 2014, there were 268 cases reported from three provinces: 210 (78.4%) from Ontario (PHO), CHEO, and HRLMP); 45 (16.8%) from Alberta; and 13 (4.9%) from British Columbia. New Brunswick, Northwest Territories, Nunavut and Yukon had no cases to report with specimen collection dates during the month of September 2014. Of note, public primary and secondary schools had been closed in British Columbia due to a teachers' strike, with schools only having resumed from summer recess on September 22, 2014 (18). Data collection was performed by Alberta Health and BCCDC using the enhanced CRF, by PHO using the PHO Laboratories General Test Requisition (23), and by CHEO and HRLMP by review of medical and laboratory records. Close to half of all cases (119 or 44.4%) had EV-D68 positive specimens collected in week 38 (September 14–20, 2014), while 60 (22.4%) and 45 (16.8%) had positive specimens collected in weeks 39 (September 21–27) and 37 (September 7–13), respectively (**Figure 1**).

Figure 1: Hospitalized pediatric (≤18 years) cases of EV-D68 by specimen collection week, EV-D68 Severe Outcomes Surveillance Pilot, Canada, September 2014



*Note: Week 40 does not include a full week of data. In addition, this epicurve represents a time-limited snapshot of hospitalized pediatric cases for September 2014, and may not be representative of the entire Canadian EV-D68 outbreak, continuing after this period.

Characteristics of cases

Of the 268 cases with specimen collection dates in September 2014, 174 (64.9%) were male; the sex difference was statistically significant (p<0.01) (**Table 1**). Of the cases where age was available (n=255), the mean age was 5.2 years (5.4 for males and 5.3 for females) and the median was 4.8 years (5.0 for males and 5.0 for females). The distribution of cases by age group is presented in the table. Half of the cases (50.6%) were in children <5 years of age and roughly a third of the cases (35.7%) were between the ages of 5 and 9. In comparing the number of cases observed in young children (<5 years) and those between 5 and 18 years of age, the difference was statistically significant (p<0.01). The number of cases observed in young children (n=129) was twice the number expected based on the population distribution.

Table 1: Descriptive epidemiological summary of hospitalized pediatric EV-D68 cases, EV-D68 Severe Outcomes Surveillance Pilot, Canada, September 2014

(N=number for which information was available)	n	%
Sex (N=268)[a]		
Male	174	64.9
Female	94	35.1
Age group (N=255)		
<2 years	56	22.0
2–4 years	73	28.6
5–9 years	91	35.7
10–14 years	31	12.1
15–18 years	4	1.6
Admitted to intensive care unit (N=266)		
Yes	18	6.8
No	248	93.2
Clinical presentation (N=231)		
Respiratory illness only	227	98.3
Neurologic illness only	1	0.4
Respiratory and neurologic illness	2	0.9
No respiratory or neurologic illness	1	0.4

[a] Difference between males and females was statistically significant (p <0.01).

Of the 266 cases for whom ICU admission status was known, 18 (6.8%) were admitted to an ICU. Of these 18 cases, 66.7% (n=12) were male and the sex distribution was similar to the distribution for all cases. The mean (5.5) and median (5.6) ages for ICU-admitted cases were slightly higher than the mean and median for all cases. Compared to the mean and median age for all cases by sex, these values were higher for males admitted to ICU (mean=6.4, median=6.0) and lower for females admitted to ICU (mean=4.0, median=3.6). Of the cases with clinical presentation data available (n=231), respiratory illness was present in 229 cases (99.1%), and neurologic illness was present in 3 cases (1.3%). Of these three cases, one presented with seizures, one with symptoms of acute flaccid paralysis, and the other with unspecified neurologic symptoms. There was one case that presented with neither respiratory nor neurological symptoms. Of the 90 cases with additional clinical information available, 39 (43.3%) were reported as having asthma. No deaths were reported among the 268 cases.

Conclusion

Outbreaks of EV-D68 had not been detected in Canada prior to 2014. Initial outbreaks of an emerging pathogen are typically first recognized on the basis of their most severe presentations and can skew the impression of overall severity associated with that pathogen. Enhanced surveillance on a population level expands the understanding of the spectrum of illness to include milder presentations, even among hospitalized cases.

Whereas a very high proportion of pediatric cases required intensive care in the initial hospital clusters detected in Kansas City (100%) and Chicago (91%) in August 2014 (13), this represents only a subset of all cases that likely occurred within the geographic catchment area of those hospitals. Similarly, our enhanced surveillance, although conducted across seven provinces and three territories, includes only laboratory-confirmed cases of EV-D68 that were hospitalized. Looking at these hospitalized cases, we report here a median age (4.8 years) consistent with what was seen initially in Kansas City (4 years) and Chicago (5 years) (13). The interesting male preponderance we report is also consistent with other surveillance summaries of enterovirus-infected persons elsewhere (9). As with other enteroviruses, it is likely that a large proportion of milder community cases occurred for which no medical visit or diagnostic testing was sought or required at all, and these mild presentations and their accompanying epidemiologic characteristics will be missed almost entirely in most surveillance summaries.

While the majority of cases observed since September 2014 have been among those 18 years of age and younger, there have also been a small number of adult cases reported (5, 17, 18), but are not included here It was decided that to provide an early snapshot of the outbreak, and for consistency across participating jurisdictions, this epidemiological summary would be restricted to pediatric cases from September 1 to 30, 2014, only. The decision to focus on pediatric populations was supported by the growing body of evidence showing that EV-D68 disproportionately affects younger populations compared to adults (6–8, 10–13, 16, 24–27). Cases in Canada have been observed beyond September, and in British Columbia, where a teachers' strike delayed the autumn return to school, a later seasonal peak in EV-D68 was observed. Therefore, ongoing surveillance in pediatric and adult populations will be important to develop a fuller understanding of disease seasonality, age-related susceptibility, and severity.

There are limitations to these data. This epidemiological summary is focused on a specific population (high-risk) and a period early in the outbreak, and may not be representative of the full EV-D68 outbreak in Canada in 2014. In addition, for those cases for which ICU admission was reported, it is unknown the extent to which EV-D68 infection contributed to the ICU admission. Also, jurisdictions conducted laboratory testing for EV-D68 using different methods that inherently provide varying levels of sensitivity and specificity (19, 28). Given that EV-D68 is not a notifiable disease nationally or within provinces and territories, some jurisdictions faced early obstacles in conducting enhanced case follow-up and reporting, and differed in their approaches to data collection. This may explain a portion of the missing results in this report and likely resulted in cases that were missed for follow-up. Similarly, jurisdictions vary in their surge capacity to respond to unexpected and emerging public health events. The EV-D68 experience is a reminder that timely public health response requires supportive legislation and infrastructure to enable the investigation of emerging pathogens which, by their very nature, occur without advance notice and may not be specifically pre-named in notifiable disease lists.

The EV-D68 Severe Outcomes Surveillance Pilot represents the first attempt to describe the epidemiological characteristics of severe pediatric cases of EV-D68 at the national level in Canada, and provides valuable insights into the early stages of the 2014 outbreak. Limitations of these findings should be considered in any attempts to extrapolate to the "Canadian" experience or in comparisons with other jurisdictions. Continued investigation is warranted to more fully define the seasonality, susceptibility and spectrum of illness associated with this emerging pathogen and to develop appropriate public health measures to mitigate its impact.

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Conflict of interest

None

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None

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FluWatch summary: February 8–14, 2015 (Week 6)

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Abstract

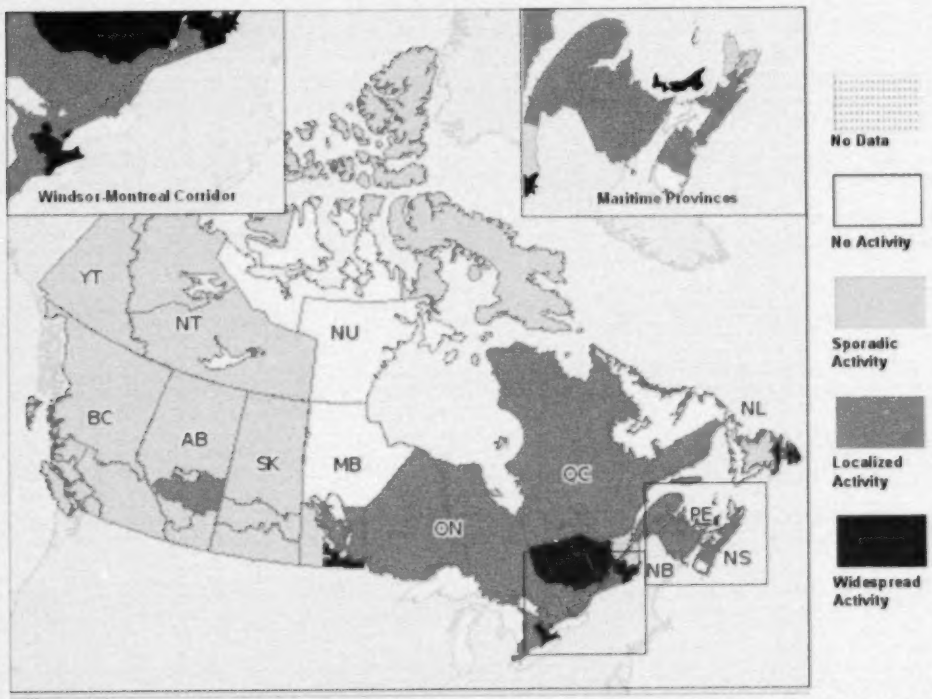
Objective: To provide a summary of the weekly *FluWatch* report on influenza activity in Canada for the week of February 8-14, 2015.

Methods: The *FluWatch* programs consists of a network of sentinel laboratories, sentinel primary care practices, provincial and territorial ministries of health, and sentinel hospitals that report on the seven main influenza indictors on a weekly basis across Canada. Information is aggregated by the *FluWatch* program and disseminated through weekly reports during the activity influenza season and bi-weekly reports during the low season.

Results: In week 6, influenza activity levels declined for six surveillance indicators. Seven regions reported widespread activity: Ontario (2), Quebec (2), Manitoba (1), Prince Edward Island (1) and Newfoundland (1). Twenty-one regions reported localized activity: New Brunswick (7), Nova Scotia (5), Ontario (5), Alberta (1) and Manitoba (1), and 22 regions reported sporadic activity. The national influenza-like-illness (ILI) consultation rate decreased from the previous week to 44.5 consultations per 1,000, which is higher than expected levels for week 6. A total of 74 outbreaks have been reported this week and the majority of outbreaks this season have been reported in long-term care facilities (LTCF). Laboratory detections of influenza decreased from the previous week from 1,884 in week 5 to 1,625 in week 6. The number of positive respiratory syncytial virus (RSV) tests decreased to 914 RSV detections down from 1,110 RSV detections in week 5 and remains the second most frequently detected virus after influenza. To date, 4,817 influenza hospitalizations and 342 deaths have been reported through the national severe outcome surveillance system; with the majority reported in adults aged 65 and over. In the 2014-15 season, the National Microbiology Laboratory (NML) has characterized 194 influenza viruses and found that the majority of influenza A (H3N2) specimens tested to date was not optimally matched to the vaccine strain; but all those tested for resistance were all found to be sensitive to oseltamivir and zanamivir. Two Canadian studies, one by the Sentinel Physician Surveillance Network (SPSN) and the other by the Canadian Immunization Research Network (CIRN), examined mid-season data on the current influenza vaccine's effectiveness and both studies observed little to no vaccine protection against the A(H3N2) virus. (See ID News)

Conclusion: Influenza A (H3N2) continues to be the most common type of influenza affecting Canadians. In laboratory detections, hospitalizations and deaths, the majority of cases have been among seniors greater than 65 years of age. The patterns of many indicators such as laboratory detections and outbreaks have been similar to the 2012-13 season when influenza A (H3N2) also predominated. The NML and the SPSN study have found that the majority of the circulating influenza A (H3N2) specimens are not optimally matched to the vaccine strain. Several indicators have been continuously declining since week 1, indicating that the peak of the 2014-15 influenza season has passed. The *FluWatch* surveillance system will continue to monitor influenza activity throughout the remainder of the 2014-15 season and publish findings in the *FluWatch* report.

Figure 1: Map of overall influenza/ILI activity level, by province and territory, Canada, Week 6 2015 (1)



Note: Influenza/ILI activity levels, as represented on this map, are assigned and reported by provincial and territorial Ministries of Health, based on laboratory confirmations, sentinel ILI rates and reported outbreaks. Detailed definitions of the different levels of activity and for maps from previous weeks, including any retrospective updates, are available on the FluWatch website.

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Conflict of interest

None

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National surveillance for non-polio enteroviruses in Canada: Why is it important?

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Abstract

A widespread outbreak of enterovirus D68 (EV-D68) was detected in association with respiratory illness in children across Canada and the United States during the autumn of 2014. The majority of cases were mild, but some were associated with more severe illness requiring hospitalization; some of the cases also had neurological symptoms including paralysis, and three deaths were reported in British Columbia. EV-D68 is one of many enteroviruses that include Coxsackieviruses, echovirusesand polio virus. Other than polio virus, there are no vaccines available for the prevention of enterovirus infections, nor are there any antiviral medications that have been approved for their treatment. More than 46 different serotypes have been identified to be circulating in Canada over the last 25 years. Until 2014, EV-D68 was rare. Routine genotyping surveillance done by Canada's National Microbiology Laboratory (NML) identified only 85 isolates of EV-D68 between 1991 and 2013, while 282 were detected between July and October 2014. The complexity of the epidemiology of these enteroviruses demonstrates the need for genotype surveillance, to detect outbreaks spatially and temporally, to determine their relative incidence and impact on the population, and to investigate evolutionary trends, such as recombination events, that are thought to play an important part in strain variation and emergence of epidemic strains. In particular, it is important to carry out virological testing on unusual cases of paralysis in children, and to genotype and sequence any viruses identified. Submission of specimens (virus cultures, stool, cerebrospinal fluid or respiratory specimens) from any such cases to the National Centre for Enteroviruses at NML is encouraged.

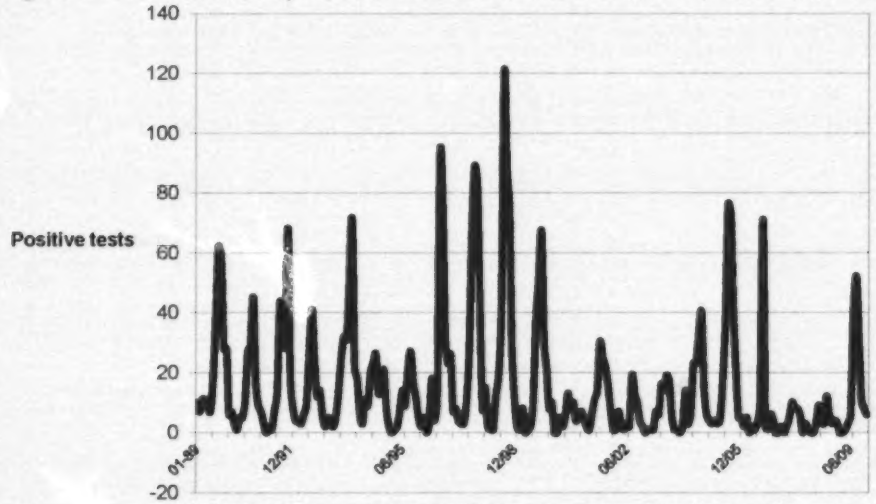
Introduction

Enterovirus D68 (EV-D68) captured public attention between August and October of 2014 when a widespread outbreak was detected in association with respiratory illness in children across Canada and the United States (1–6). The majority of cases were mild and involved influenza-like symptoms, such as fever, cough, rhinitis, pharyngitis, bronchitis and myalgia. A proportion of these cases of EV-D68 infection were associated with more severe illness requiring hospitalization. The hospitalized cases involved pneumonia, bronchiolitis and respiratory distress, and underlying asthma appeared to be the main risk factor. Some of the cases also had neurological symptoms including paralysis, and three deaths were reported in British Columbia (6). In the United States, the Centers for Disease Control and Prevention (CDC) tested about 2,600 specimens for EV-D68 during the late summer of 2014 and found that about 36% of them were positive for the virus, including 12 patients who died, and the infection was confirmed in 1,152 patients in 49 states (7). In Canada, the National Microbiology Laboratory (NML) tested 970 specimens for EV-D68 and identified 282 positive cases between August and October of 2014. It has been suggested that the EV-D68 outbreak in the United States could be related to an increase in cases of acute flaccid myelitis, an unexplained neurological illness involving limb weakness in children that coincided with the increased detection of EV-D68 (8). The purpose of this article is to provide an overview of the complexity of the aetiology and epidemiology of non-polio enterovirus diseases and to identify why it is important to track this group of infections. There is a need to carry out further laboratory-based epidemiological surveillance for possible links between enterovirus infection and emerging paralytic illnesses.

Enteroviruses belong to the picornavirus family, a large and diverse group of small ribonucleic acid (RNA) viruses characterized by a single positive-strand genomic RNA, and include four major species, A, B, C and D, of which polio virus strains are members of the C group (9). Poliovirus thus shares many biochemical and physical

characteristics with other human enteroviruses (which include Coxsackieviruses, echoviruses, and rhinoviruses: the latter are common cold viruses). Non-polio enteroviruses cause many clinical syndromes, notably hand-foot-and-mouth disease, aseptic meningitis, flaccid paralysis, myocarditis, pneumonia and respiratory disease, fevers, gastroenteritis, hepatitis, and pancreatitis. Most of these infections affect children disproportionately, and many are potentially fatal. It is also likely that enterovirus infections are highly under-diagnosed, since laboratory testing is often not carried out. Other than polio virus, there are no vaccines available for the prevention of enterovirus infections, nor are there any antiviral medications that have been approved for their treatment. In Canada, as in many temperate regions, enterovirus infections peak in the late summer and early autumn months (**Figure 1**). Enteroviruses are usually transmitted by a faecal-oral route, through contaminated water supplies, and by close contact with infected persons. Enteroviruses can be detected in stool specimens, respiratory specimens, and are also found in cerebrospinal fluid specimens of infected persons (10). Many enteroviruses including EV-D68 are also shed in respiratory secretions suggesting that a respiratory route of infection is also involved in the transmission of EV-D68. So far there are no reports of finding EV-D68 in the nervous system which could provide a hypothetical mechanism to explain the possibility of neuropathogenic effects including paralysis.

Figure 1: The seasonality of echovirus infections in Canada, from 1990 to 2009[a]

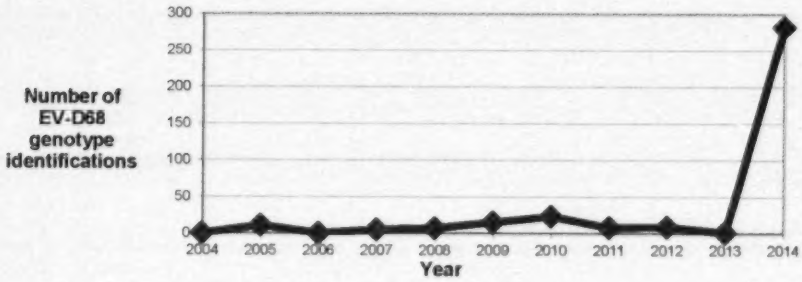


[a]Monthly data of positive test identifications from the Canadian virus reporting system (11).

Enterovirus surveillance in Canada and the emergence of EV-D68

EV-D68 was rarely identified in Canada between1990-2014. Routine genotyping surveillance done by the National Centre for Enteroviruses at the Public Health Agency of Canada's National Microbiology Laboratory identified only 85 isolates of EV-D68, Then there were 282 positive cases out of 970 tested occurred between July and October of 2014 (**Figure 2**). EV-D68 is usually associated with respiratory infections and mild cold-like illnesses, but there are reports that it has occasionally been associated with more acute respiratory diseases in children, and rarely in association with central nervous system disease (12). Outbreaks of EV-D68 infection in children were detected in 2009 and 2010 in many parts of the world (12–19). In Canada, there is evidence from our laboratory genotyping surveillance that minor outbreaks of EV-D68 also occurred during 2009 (15 cases) and 2010 (23 cases) (**Figure 2**).

Figure 2: Numbers of cases of EV-68 infection identified in Canada by molecular genotyping at the National Microbiology Laboratory, 2004–2014



The NML routinely genotypes enterovirus specimens of as part of its diagnostic services; this testing also has the added benefit of providing surveillance data on the incidence of various enterovirus serotypes in Canada over the years, and an ability to quickly identify any unusual outbreaks. More than 46 different serotypes have been identified to be circulating frequently in Canada over the last 25 years. Data for the 20 most prevalent enteroviruses are shown in **Table 1**. A year-by-year analysis shows periodic peaks and lows for each serotype: echovirus 30 is the most common non-polio enterovirus circulating in Canada and there were major outbreaks in 1998, 2006 and 2009. Echovirus 7 caused an outbreak in 2002, and there was a peak of echovirus 5 in 2007. Coxsackievirus A16 (CV-A16) is the most common cause of hand-foot-and-mouth disease; and CV-A9, which is also commonly circulating in Canada and is associated with these disease outbreaks, had a major peak of laboratory identifications in 2003.

Table 1: The number of virus isolations for the 20 most prevalent enterovirus genotypes in Canada from 1991 to 2013, in surveillance carried out by the National Centre for Enteroviruses, National Microbiology Laboratory

Enterovirus serotype	Total isolations	% of total
Echovirus 30 (E-30)	408	15,5
Coxsackievirus A16 (CV-A16)	196	7,5
Echovirus 11 (E-11)	183	6,9
Coxsackievirus (CV-A9)	177	6,7
Echovirus 18 (E-18)	149	5,6 %
Echovirus 25 (E-25)	137	5,2
Echovirus 9 (E-9)	116	4,4
Coxsackievirus (CV-B4)	111	4,2
Coxsackievirus (CV-B3)	104	3,9
Enterovirus A71 (EV-A71)	101	3,8
Coxsackievirus (CV-B2)	98	3,7
Coxsackievirus (CV-B5)	97	3,6
Echovirus 6 (E-6)	97	3,6
Enterovirus D68 (EV-D68)	85	3,2
Echovirus 7 (E-7)	83	3,1
Coxsackievirus (CV-B1)	80	3,0
Echovirus 5 (E-5)	77	2,9
Echovirus 4 (E-4)	58	2,2
Echovirus 22	45	1,7
Echovirus 3 (E-3)	34	1,3

The case for surveillance

Genotype surveillance is needed because of the complexity of the epidemiology of these enteroviruses, both in the wide variety of genotypes that are present in the population and in the diverse range of diseases that they are associated with. The aim is to detect outbreaks spatially and temporally and to determine their relative incidence and impact on the population. In addition, this surveillance gives warning of emerging infections such as EV-A71 and EV-D68, as well as the capability to follow genetic evolution in strains that could be associated with increased pathogenicity. In particular, it will be important to carry out virological testing on unusual cases of paralysis in children, and to genotype and sequence any viruses identified. We encourage submission of specimens from any such cases to the enterovirus section at NML. Ideally these specimens can be virus cultures, but cerebrospinal fluid, stool or respiratory specimens are also suitable. We also need to maintain vigilance for polio virus now that we are at a critical point in the global eradication of poliomyelitis.

Acute flaccid paralysis and non-polio enteroviruses

Acute flaccid paralysis (AFP) is defined as sudden onset of reduced muscle tone and weakness without obvious cause (i.e., trauma) and is usually characterized by looseness and flexibility in limbs, and a lack of strength in moving and controlling the muscles. It may be caused by Guillain-Barré syndrome (an autoimmune disorder affecting the peripheral nervous system), and by a number of agents including poliovirus, some non-polio enteroviruses, echoviruses, adenovirus, West Nile virus, and campylobacter infections. Any part of the body can be affected—not only the limbs—and this may result in difficulty in breathing, suffocation and death. Thus, AFP has a very broad clinical syndrome, can have a wide range of causes, and c ı appear similar to other neurological syndromes, including, for example, transverse or anterior myelitis and traumatic neuritis (20).

It is well known that non-polio enteroviruses, such as Coxsackieviruses, echoviruses, and many enteroviruses, including types 70, 71, 89, 90, 91, 96, 99, 102, and 114, are associated with numerous neurological clinical manifestations, such as encephalitis, meningitis and paralytic disease, including AFP-like syndromes (21). Of these viruses, EV-A71 has been found to be the most commonly associated with non-polio flaccid paralysis (20) and with neurological disease, including fatal encephalomyelitis (22). EV-A71 emerged during the 1990s as an agent that causes periodic, extensive outbreaks of hand-foot-and-mouth disease in children in China and other parts of Asia (23), and the viral sub-genotypes involved in these outbreaks also spread throughout Southeast Asia and Australia. An outbreak of EV-A71 in Taiwan in 1998 caused 1.5 million infections and 78 deaths (23). A particularly large outbreak of EV-A71 occurred in China in 2009; although the total number of cases was not reported in all provinces, it was clear that a small proportion of these developed severe complications that included neurological symptoms and deaths (24). Nevertheless, severe cases of EV-A71, especially with neurological involvement, are relatively rare, and most children affected recover completely. Antivirals that are effective for this class of viruses are still at the development stage. Efforts are also underway to develop vaccines for the control of continuing EV-A71 outbreaks in Asia. In addition to hand-foot-and-mouth disease, non-polio enterovirus infections are also the likely cause of about 50% of all cases of aseptic meningitis (25). Thus, there is already a great deal of evidence that enterovirus infections can cause neurological diseases including paralysis.

A pilot study in Canada during September 2014 in seven provinces and territories collected epidemiological data for 268 hospitalized cases of EV-D68 infection and found only 3 neurological cases and no deaths (26). The rarity of these neurological cases means that much larger population studies will be needed to more fully investigate the possible link between EV-D68 and paralysis. One difficulty is that, other than polio, enterovirus infections are not nationally notifiable in Canada, and so the true number of laboratory-confirmed cases may not be reported. In addition, the true incidence of infection is likely to be much higher than the numbers of laboratory-confirmed cases, since the majority of infections never undergo virological testing. Therefore, it will be important to continue this enhanced surveillance during the next enterovirus season in 2015, to determine if EV-D68 returns and, if so, to measure its impact on the population, especially in children. More severe cases of non-polio enterovirus infection may also be identified through Canada's AFP surveillance system, or through the NML's national enterovirus genotype surveillance program. It is thus important to continue with these laboratory-based virological surveillance systems to be able to detect further emerging enterovirus disease, should it occur in Canada.

Conclusion

The identification of associations or causal links between enterovirus disease outbreaks and more serious illnesses such as paralysis have posed some challenges that can only be addressed by additional widespread surveillance. This should involve the collection of comprehensive clinical and epidemiological data in conjunction with laboratory testing that includes molecular typing and sequencing of the viruses. Although there is no proven link between EV-D68 and paralysis in children, enteroviruses are well known as agents that are associated with neurological illnesses and paralysis in a small proportion of infected cases. The emergence of an enterovirus, EV-D68, that was hitherto rarely identified as a cause of illness, as an agent that is capable of causing widespread outbreaks of mild to severe respiratory disease, is a new health risk that warrants continued investigation and close monitoring. A next step is to increase the number of specimens submitted for enterovirus typing, and to improve the level of clinical epidemiological data included in these submissions. Ideal specimens for enterovirus testing are virus cultures, stool, cerebrospinal fluid or respiratory swabs or aspirates. Surveillance for non-polio enteroviruses helps to improve confidence in Canada's polio-free status, as well as identifying the incidence and

impact of enteroviruses on health and for monitoring for emerging agents that pose a new risk to health such as EV-D68 and EV-A71 viruses.

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Conflict of interest

None.

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Canadian vaccine research networks: Vaccine safety resources for Canada

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Abstract

The Public Health Agency of Canada / Canadian Institutes of Health Research Influenza Research Network (PCIRN), established in 2009 to undertake evaluative research to inform public health decision making in Canada, is now being replaced by the Canadian Immunization Research Network (CIRN), which will retain the mandate of PCIRN but expand it to all vaccines including influenza vaccine. CIRN is organized as a network of networks focusing on undertaking research in the areas of vaccine safety, adverse events following immunization (AEFIs), vaccine hesitancy, vaccine effectiveness, and vaccine coverage. CIRN's networks include: a clinical trial network; a laboratory network; a modelling and economics network; a network of social science and humanities researchers; a vaccine safety surveillance network; a hospital-based surveillance network; a clinic network to evaluate serious AEFIs; and a network that links vaccine research capacity in provincial health agencies and departments. PCIRN has contributed to Canada's vaccine safety surveillance system and has facilitated the translation of safety research into policy. Vaccine safety surveillance and research will remain a focus of the newly formed Canadian Immunization Research Network.

Introduction

The Public Health Agency of Canada (PHAC) / Canadian Institutes of Health Research (CIHR) Influenza Research Network (PCIRN) was designed to consolidate the existing expertise in influenza vaccine evaluation, increase capacity to rapidly test influenza candidate vaccines, develop links between researchers and decision makers, and train influenza researchers. In 2013, PHAC and CIHR announced that they would fund a Canadian Immunization Research Network (CIRN), with a mandate to undertake evaluative vaccine research, including research related to influenza vaccine formerly undertaken by PCIRN. Currently, CIRN represents over 100 investigators from more than 40 Canadian institutions, comprising experts in vaccine-related evaluative research from a wide array of disciplines. The objective of this article is to describe how PCIRN contributed to vaccine safety intelligence in Canada in the past and how CIRN will take over and expand this mandate in the future.

PCIRN overview and research networks

PCIRN was designed as a "network of networks." From its inception in 2009, PCIRN has addressed important issues related to influenza vaccine programs.

The Clinical Trials Network

The Clinical Trials Network has sites in Vancouver, Calgary, Winnipeg, Sudbury, Hamilton, Toronto, Ottawa, Montréal, Québec City and Halifax, and has the capability to conduct rapid clinical trials in large and specialized groups with a focus on safety, immunogenicity and mechanisms of immunity.

Canadian National Vaccine Safety Network (CANVAS)

The Canadian National Vaccine Safety Network quickly gathers and analyzes safety data on thousands of vaccinated individuals (adults and children) to provide influenza vaccine safety information to public health authorities before the core weeks of the annual influenza vaccination campaign. Participants are recruited from acute care and public health influenza vaccination clinics in five provinces. Participants receive a short electronic survey eight days after their vaccination. The main outcome is the occurrence of any new health problem or the exacerbation of an existing condition that is severe enough to cause work or school absenteeism and/or prevent daily activities or to require a medical consultation. Selected severe reported events are followed up by telephone for additional details. A control group of unvaccinated participants is also recruited each year to determine the frequency of reported events in an unvaccinated group (i.e., the background rate).

Special Immunization Clinics Network

The Special Immunization Clinics Network is a national network of expert clinicians in 13 hospitals across Canada who accept referrals from public health professionals or clinicians for individual patients who have experienced an adverse event following immunization (AEFI) or who have another vaccine safety issue. Its first objective is to standardize clinical care and guide best practice in the management of these patients. The standardization of clinical care provides opportunities for observational research. The second objective is to establish a platform for research studies on vaccine safety issues.

Serious Outcomes Surveillance (SOS) Network

The (SOS) Network, conducts active surveillance for influenza requiring hospitalization in Canadian adults. This surveillance covers more than 18,000 beds in 45 hospitals in seven provinces. The SOS Network is designed to measure disease burden and to assess vaccine effectiveness in the prevention of influenza-related hospitalization and death.

Program Delivery and Evaluation Network

The Program Delivery and Evaluation Network engages in applied public health research related to the delivery of influenza vaccines. This Network will conclude its work at the end of the PCIRN funding period.

Reference Laboratory Network

The Reference Laboratory Network includes five laboratory sites across Canada and is managed by scientists with expertise in microbiology, influenza, and other infectious diseases. Each scientist leads active research programs at his respective institution and also operates within the public health sector. The Network provides influenza-related laboratory testing support for the Network and manages PCIRN's biorepository.

PCIRN's record of vaccine safety studies

While PCIRN's influenza research mandate is broad, vaccine safety research has been a major focus for several of its networks. The Clinical Trials Network has completed eight clinical trials to date, many of which had a vaccine safety focus. The PCIRN clinical trials in 2009 with the adjuvanted pandemic vaccine measured adverse events in different population groups, including healthy adults (1), Aboriginal populations (2), and individuals with human immunodeficiency virus (HIV) infection (3). In 2010, there was concern that previous recipients of the adjuvanted H1N1 pandemic vaccine might have increased rates of injection-site and systemic adverse events when they received the seasonal trivalent inactivated vaccine containing the pandemic strain, because of very high levels of pre-existing antibodies. Two clinical trials, one in adults and one in children, were performed as soon as the vaccine was made available and results were presented to decision makers and program planners in advance of the roll-out of the annual influenza vaccine campaigns (4, 5). The vaccination of egg-allergic individuals with influenza vaccine was also a major safety research focus of PCIRN and provided data that led to a significant change in vaccination recommendations (6, 7). The success of these safety studies led to the development of the Special Immunization Clinics Network, which will continue its work under CIRN.

The Canadian National Vaccine Safety Network also contributed safety information about influenza vaccines over the last several years (8, 9). For the 2013–2014 season, CANVAS reached record recruitment, enrolling over 35,000 adults and parents of children. The response rate was 61% (n=13,127) in the vaccinated group and 50% (n=6,763) in the control group. Parents of children 6 months to 16 years of age accounted for 12% (n=2,314) of participants. The vast majority of participants reported no health events (96% of vaccinees and 93% of controls). In the control group 5% reported an event that caused absenteeism, prevented daily activities, or required a medical consult, while 2.5% of vaccinees reported such events. The remaining events (2% in controls and 1.5% in vaccinees) were reported as uncomfortable or easily tolerable. Regardless of vaccination status, the most frequently reported symptoms in adults and children were respiratory and gastrointestinal symptoms, and these symptoms occurred more frequently in controls than in vaccinees. In children, changes in eating patterns were reported more frequently among vaccinees. No deaths or hospitalizations were reported among vaccinees or controls. Fewer than 1% of vaccinees (0.4%) and 1% of controls reported medical consultation for their symptoms, and among those the rate of emergency department visits was the same in both groups (0.53 per 1,000 participants). With the ability to detect events occurring at a rate of less than 1 in 1,000, we did not find any safety signals associated with 2013–2014 influenza vaccines in adults or children. In the event a signal is detected, CANVAS has the ability to link with public health authorities and conduct additional enhanced follow-up.

Following the release of the adjuvanted pandemic influenza vaccine in Canada in 2009 and during the immunization campaigns of 2010–2011, the SOS Network conducted active surveillance for adverse events of special interest. Surveillance monitors in all participating hospitals reviewed all admissions to medical services, intensive care units, and hematology and neurology services daily to identify patients admitted with Guillain-Barré syndrome, idiopathic thrombocytopenic purpura (ITP), or encephalitis meeting the Brighton Collaboration case definitions and with symptom onset within six weeks of receipt of an influenza vaccine. No cases of AEFIs were identified in participating hospitals during the surveillance period.

CIRN overview and networks

Like PCIRN, CIRN will be a "network of networks." As PCIRN funding ends in 2015, several of its network infrastructures will become part of CIRN and will be joined by several new networks to meet CIRN's expanded mandate.

The Special Immunization Clinics Network, which was created during PCIRN's renewal term, will not require any transition into CIRN because it was designed to undertake standardized evaluation of AEFIs related to all vaccines, not just influenza. In its first year, investigators reviewed the literature on the risk of recurrence of AEFIs and prepared a clinical management guide. The Network currently recruits patients for its core study which will evaluate the risk of revaccination in patients previously affected by an AEFI and the risk of administering vaccines in patients with underlying conditions that may constitute an apparent contraindication.

The Clinical Trials Network will transition easily from PCIRN to CIRN since all of the sites have experience with clinical trials unrelated to influenza vaccine.

The SOS Network will transition from PCIRN to CIRN and provide CIRN with hospital-based surveillance and the ability to measure vaccine effectiveness. Although focused primarily on describing the burden of influenza and the effectiveness of influenza vaccine against severe disease, the SOS Network has already leveraged industry funding to measure the burden of invasive meningococcal disease, community-acquired pneumonia, and invasive pneumococcal disease in adults.

While initially created to assess vaccine safety immediately after implementation of annual influenza vaccine campaigns, the Canadian National Vaccine Safety Network will be leveraged for studies related to safety of other vaccines used in these cohorts, evaluation of vaccine hesitancy, and vaccine effectiveness.

The Reference Laboratory Network will transition from PCIRN to CIRN, and will continue to actively manage a sample archive of sera and other biological samples collected through CIRN infrastructures, accessible to investigators for future studies. The Network will also encompass the Immunity of Canadians and Risk of Epidemics (iCARE) Network. The Reference Laboratory Network spans five provinces and coordinates the

matching of laboratory capabilities from participating academic and public health laboratories with CIRN project needs.

Provincial Collaborative Network

The Provincial Collaborative Network is a new network created under CIRN that will capitalize on the extensive research capabilities in provincial public health agencies and other provincial departments of health and provide a collaborative platform in which to undertake evaluative, programmatic, applied public health research. The Network will develop common methodologies to assess vaccine safety, effectiveness, and coverage, including the use of aggregate and linkable individual-level data contained in a variety of existing databases within each province (e.g., reportable disease, laboratory, immunization, health care utilization, and vital statistics data). This approach is analogous to the U.S. Vaccine Safety Datalink and the Canadian Network for Observational Drug Effect Studies (10). Current investigators are based in 7 of 13 provinces/territories. We hope to include others in the future and build on the methodology developed in our initial studies.

Social Sciences and Humanities Network

CIRN's new Social Sciences and Humanities Network will link social scientists and humanities researchers across Canada to examine the ethical, legal and social implications of vaccine programs and CIRN-related research. The Network will enhance CIRN's ability to address societal issues in all proposed projects and will serve as a hub for social science and humanities-focused research generated by CIRN; vaccine hesitancy will be a major focus.

Modeling and Economics Research Network (ModERN)

CIRN's newly created Modeling and Economics Research Network will link modellers/health economists in at least five provinces to undertake epidemiological analyses, mathematical modelling, and economic analysis to study the cost-effectiveness and population-level effectiveness of public health interventions. ModERN can also investigate the likelihood of outbreaks based on coverage; predict the magnitude of impact of emerging pandemics and optimal control strategies in Canada; and examine population-level concerns following introduction of vaccines about shifts in the age at infection, type replacement, and waning efficacy.

CIRN projects involving vaccine safety

The Clinical Trials Network of CIRN, arising from PCIRN's rapid clinical trials network, now has the requisite training and infrastructure to respond to public health issues concerning vaccine-preventable diseases by developing high quality research protocols to evaluate vaccines, implement them quickly and in accordance with regulatory and international standards, and rapidly provide results on vaccine safety at various time points during and after the trial is complete. The trials planned for the 2014–2017 CIRN funding cycle will address two important vaccine-preventable diseases: hepatitis B and invasive meningococcal disease (*Neisseria meningitidis*). One project will determine whether youth immunized with hepatitis B vaccine as infants continue to have serologic evidence of immunity and, if not, whether a booster dose of vaccine will elicit antibodies produced because of anamnestic immune memory. In a second randomized, controlled, double-blind clinical trial, the safety and immunogenicity of an accelerated schedule for a four-component meningitis B vaccine will be evaluated. Outcome measures for vaccine safety will be incorporated into both studies, capturing information on solicited local injection-site and systemic AEFIs, unexpected unsolicited adverse events, as well as tolerability. The Clinical Trials Network will work with other CIRN researchers to test novel tools to measure AEFIs, such as a smartphone application which will facilitate the electronic capture of AEFI data.

The methodology employed by CANVAS for monitoring AEFIs after influenza vaccination is well adapted to monitoring the safety of other vaccines. CIRN protocols are being developed that would adapt CANVAS to safety reporting for new vaccines, such as the new meningococcal B vaccine.

The Special Immunization Clinics Network will act as a platform for multicentre clinical studies relevant to vaccine safety. Within CIRN, the Network's initial focus will be on vaccination of immunocompromised patients. The first project will enroll children who have completed chemotherapy for acute lymphoblastic leukemia (ALL) or who have received a stem cell transplant (SCT). The objectives are to a) describe institutional immunization practices at pediatric oncology and SCT centres through a survey; b) identify risk factors for low vaccine titres in children treated for ALL; c) identify clinical and immunologic factors that influence vaccine responses in pediatric ALL and post-SCT patients; and d) determine the frequency of AEFIs in both groups. This study will be conducted at the

Special Immunization Clinics Network sites, using similar approaches to patient assessments and follow-up as those developed under PCIRN. The findings will help support the development of immunization guidelines for children with ALL and harmonize immunization practices for pediatric SCT recipients. If successful, the methodology will be expanded to other populations of immunocompromised patients. The Network will continue to build capacity to evaluate new and emerging vaccine safety signals and will thus contribute to pandemic preparedness. Future studies could include selected AEFIs requiring investigation in real time, the study of the biologic mechanisms involved in AEFIs, or the study of the genetic basis of particular events in collaboration with other similar networks.

One of the Provincial Collaborative Network's initial studies will examine safety issues of relevance to Canada. In the project "Assessing rotavirus vaccine safety in Canada with regard to intussusception using administrative databases," researchers plan to take a pan-Canadian approach using health administrative data to determine the background rate of intussusception in Canadian infants and examine whether there has been a change in incidence following the introduction of publicly-funded rotavirus vaccination programs. This study will demonstrate the capability of the Network to conduct relevant post-marketing safety studies and provide much needed baseline data within Canada. It will also inform decision making for jurisdictions that have yet to implement vaccination programs and provide information for risk communication for parents.

The SOS Network provides important infrastructure for targeted surveillance for AEFIs and for signal assessment and hypothesis testing. With trained surveillance monitors in all participating hospitals and existing surveillance protocols and agreements in place, the SOS Network has the capacity to respond rapidly to an emerging safety signal through amendments to existing protocols. All surveillance monitors are well trained in the use of the existing SOS Network DACIMA database, and changes to data elements collected for the purpose of AEFI surveillance could be implemented rapidly to allow PHAC and the provinces/territories real-time access to observed AEFIs.

Conclusion

CIRN, like PCIRN before it, provides a national, integrated, collaborative, multidisciplinary research platform to undertake ongoing federally- and provincially-funded evaluative research that will inform public health policy and will provide the infrastructure, capacity and capability for a national research response to new and emerging infections including (but not limited to) pandemics. CIRN will also play a pivotal role in mentoring early-career researchers, providing opportunities for trainees, and delivering meaningful engagement of stakeholders at all research stages.

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Conflict of interest

Scott A. Halperin reports grants from the Canadian Institutes of Health Research (CIHR) and the Public Health Agency of Canada during the conduct of the study and grants from multiple vaccine manufacturers outside the submitted work. He serves on ad hoc advisory panels from multiple vaccine manufacturers. Gaston De Serres reports grants from GlaxoSmithKline outside the submitted work. Joanne M. Langley reports grants from GlaxoSmithKline during the conduct of the study; grants from Sanofi Pasteur outside of the submitted work; and service in a volunteer capacity on immunization/infectious disease advisory committees to the Government of Nova Scotia and the Public Health Agency of Canada. Shelly McNeil reports grants from Pfizer, GlaxoSmithKline, and Sanofi Pasteur. David Scheifele reports grants from Pfizer, Novartis, GlaxoSmithKline, and Sanofi Pasteur outside the submitted work. All other authors have nothing to disclose.

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ID News

Shaw J, Welch TR, Milstone AM. **The role of syndromic surveillance in directing the public health response to the *enterovirus* D68 epidemic.** JAMA Pediatr. 2014;168(11):981–2. doi:10.1001/jamapediatrics.2014.2628.
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"Commercially available multiplex polymerase chain reaction-based respiratory pathogen panels offer rapid detection of common pathogens with high sensitivity and specificity. Because of the nucleic acid sequence similarities between the many types of *Rhinovirus* and *Enterovirus*, most of these panels do not distinguish between these 2 virus groups and are therefore typically reported as "*Rhinovirus/Enterovirus*." These panels have proved a useful screening test during the current EV-D68 outbreaks as specimens that test positive for *Rhinovirus/Enterovirus* can prompt further analysis to specifically identify EV-D68 . . . Confirmatory testing relies on partial sequencing of the structural protein gene VP4-VP2 or VP1 region, available in some . . . laboratories."

Skowronski D, Chambers C, Sabaiduc S, De Seers G, Dickinson J, Winter AL et al. **Interim estimates of 2014/15 vaccine effectiveness against influenza A(H3N2) from Canada's Sentinel Physician Surveillance Network**, January 2015, Euro Surveill. 201 Jan 29;19(5).
http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21022

The 2014/15 influenza season to date in Canada has been characterised by predominant influenza A(H3N2) activity. Canada's Sentinel Physician Surveillance Network (SPSN) assessed interim vaccine effectiveness (VE) against medically attended, laboratory-confirmed influenza A(H3N2) infection in January 2015 using a test-negative case–control design. Of 861 participants, 410 (48%) were test-positive cases (35% vaccinated) and 451 (52%) were test-negative controls (33% vaccinated). Among test-positive cases, the majority (391; 95%) were diagnosed with influenza A, and of those with available subtype information, almost all influenza A viruses (379/381; 99%) were A(H3N2). Among 226 (60%) A(H3N2) viruses that were sequenced, 205 (91%) clustered with phylogenetic clade 3C.2a, considered genetically and antigenically distinct from the 2014/15 vaccine reference strain... Consistent with substantial vaccine mismatch, little or no vaccine protection was observed overall, with adjusted VE against medically attended influenza A(H3N2) infection of −8% (95% CI: −50 to 23%). Given these findings, other adjunct protective measures should be considered to minimise morbidity and mortality, particularly among high-risk individuals. Virus and/or host factors influencing this reduced vaccine protection warrant further in-depth investigation.

McNeil SA, Andrew MK, Ye L, Haguinet F, Hatchette TF, ElSherif M, LeBlanc J, Ambrose A, McGeer A, McElhaney JE, Loeb M, MacKinnon-Cameron D, Sharma R, Dos Santos G, Shinde V, on behalf of the Investigators of the Serious Outcomes Surveillance Network of the Canadian Immunization Research Network (CIRN). **Interim estimates of 2014/15 influenza vaccine effectiveness in preventing laboratory-confirmed influenza-related hospitalisation from the Serious Outcomes Surveillance Networks of the Canadian Immunization Research Network**, January 2015. Euro Surveill. 2015;20(5):pii=21024.
http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21024

The 2014/15 influenza season in Canada has been characterised to date by early and intense activity dominated by influenza A(H3N2). A total of 99.0% (593/599) hospitalisations for laboratory-confirmed influenza with a known influenza virus type enrolled in sentinel hospitals of the Serious Outcomes

Surveillance Network of the Canadian Immunization Research Network were due to influenza A. Of the 216 with a known subtype, influenza A(H3N2) accounted for 99.1% (n=214). Interim unmatched vaccine effectiveness (VE) estimates adjusted for age and presence of one or more medical comorbidities were determined by test-negative case–control design to be −16.8% (90% confidence interval (CI): −48.9 to 8.3) overall and −22.0% (90% CI: −66.5 to 10.7) for laboratory-confirmed influenza A(H3N2). Among adults aged under 65 years, the overall VE was 10.8% (90% CI: −50.2 to 47.0) while in adults aged 65 years or older, the overall VE was −25.4% (90% CI: −65.0 to 4.6).